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PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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14. ABSTRACT <p>The purpose of this research effort is to conduct a randomized controlled trial (RCT): "Nasal Irrigation for Chronic Rhinosinusitis and Fatigue in Patients with Gulf War Illness" which will evaluate the effects of two different types of nasal irrigation solution compared to a control group for sinus and fatigue symptoms in adults with GWI.</p> <p>The primary activities conducted during year one of the project pertain to the approval process for human subjects research activities. This requires protocol submission to the UW Health Sciences Institutional Review Board (HS IRB) and the Madison Veteran Affairs Research and Development (VA R&D) Committee. In order to proceed with human subjects research, both the UW IRB and the VA R&D require completion of separate, yet concurrent, research review and approval processes. The project was granted final VA approval on 7/16/12 following by UW HS IRB approval on 7/23/12.</p>					
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Introduction

More than 50,000 troops returned from the Persian Gulf conflicts reporting a myriad of medically unexplained symptoms with no identifiable etiology. While patients who meet the case definition of Gulf War Illness (GWI) can have a myriad of symptoms, two of the most prevalent and debilitating ones are chronic nasal congestion and fatigue. The purpose of this research effort is to conduct a randomized controlled trial (RCT): “Nasal Irrigation for Chronic Rhinosinusitis and Fatigue in Patients with Gulf War Illness” which will evaluate the effects of two different types of nasal irrigation solution compared to a control group for sinus and fatigue symptoms in adults with GWI.

Body

The major objectives of the study are twofold: 1) To find an effective adjunctive therapy for veterans with Gulf War Illness (GWI) and symptoms of chronic rhinosinusitis (CRS) and fatigue and 2) To evaluate the proinflammatory bias of each individual’s profile at baseline and in response to therapy. Statistically positive results on clinical outcome measures would demonstrate that nasal irrigation (NI) can provide effective adjunctive therapy for CRS and fatigue, improving quality of life for GWI-affected patients and potentially to society through reduced use of medical resources use and absenteeism. Positive findings on cytokine and cellular assessment would shed light on the etiology of CRS and fatigue in the GWI population and contribute to the understanding of each; positive response to therapy would elucidate a biological mechanism of action of NI. Finally, the finding that NI, adjunctive to routine care, is more cost effective than “routine care only” would provide economic justification for its clinical use in the studied population.

The primary activities conducted during year one of the project included steps relating to the infrastructure of the study and procedures to complete the approval process for human subjects research activities. One of the initial tasks in relation to the study was an application to the UW IRB for “Preparatory to Research” activities. A relatively short document was produced by the PI requesting permission to conduct work to set up the study for which a peer reviewed process has generated funding. This was completed and approved.

Study personnel proceeded to develop study related documents in preparation for study implementation following the preparatory to research approval. Study related documents developed during this time frame include:

- Scientific study protocol
- Application for UW Clinical Research Unit services
- Recruitment materials (flyer, letters, phone scripts)
- Consent documents
- HIPAA documents
- Outcome measures & surveys
- Baseline general and disease specific data collection instruments
- Transition of relationship with private sector partner Danisco to Danisco-Dupont; Study related relationship is intact.

A substantial amount of time was dedicated to the development of study documents to facilitate the human subjects research approval process.

The human subjects research approval process required protocol submission to the UW Health Sciences Institutional Review Board (HS IRB) and the Madison Veteran Affairs Research and Development (VA R&D) Committee. In order to proceed with human subjects research, both the UW IRB and the VA R&D require completion of separate, yet concurrent, research review and approval processes.

The HS IRB review process involves submission of an on-line application submitted through the Application Review for Research Oversight at Wisconsin (ARROW) system. The initial HS IRB application was submitted on 11/25/11. A key element of the submission was the approval of the UW Institute for Clinical and Translational Research - Clinical Research Unit (CRU) for studies utilizing CRU services. The CRU is the site of the initial clinical meeting with research participants and a key member of the research team. The CRU performs a protocol implementation review for any nursing, bionutrition, hospital policy, and administrative issues. Any issues identified, must be resolved, and the study approved by CRU, before reservations can be made and the study initiated. The CRU protocol review committee endorsed the study on 12/7/11.

As a result of this endorsement, and the resolution of minor administrative issues with the ARROW submission, the application moved to HS-IRB pre-review. The pre-review process entailed comments/revisions to several elements of the protocol and related documents. The pre-review was completed 3/7/12. The final UW HS IRB approval was granted on 7/23/12 following final endorsement by the VA R&D Committee.

The initial VA R&D Committee application and related documents were also submitted on 11/25/11. A preliminary step for this application process is review of the consent and privacy authorization documents by the VA Privacy Officer. The initial review of these documents was completed on 1/5/12 with comments and requests for revisions. The application was then forwarded to the VA R&D committee in mid-February. Unanticipated recruitment concerns resulted in a minor revision to the protocol. Unfortunately, the timing was such that the protocol could not be reviewed at the March VA R&D Committee meeting and was subsequently scheduled for the April meeting. Following minor revisions to the application, final R&D Committee approval was granted on 7/16/12.

We were also recently informed that the company that will provide Xylitol (Danisco) has been sold to a private company (DuPont) a large multinational corporation which has its own human subjects review process. The PI has been in active communication with Danisco-Dupont regarding continuity of study regarding procurement and packaging of xylitol packets (saches) for individual use by participants in the xylitol arm of the study. These communications have been positive and the study remains a priority of Danisco-Dupont. The PI, study personnel and Danisco-Dupont will address specific issues in an August 13, 2012 teleconference. Formal submission of the protocol to Danisco-Dupont has been made and the status will be discussed during the teleconference. Following approval by the aforementioned bodies, the protocol will need to receive final approval by the Department of Defense Human Research Protection Office prior to commencement of subject enrollment and patient-related study activities.

Regarding the procurement of xylitol, its manufacturer (Danisco) will provide xylitol in daily use packets at no cost as indicated in the protocol and letter of support in the initial grant application. This remains true though working with the ethics infrastructure of Danisco/DuPont

will add some ramp-up time. Consideration was given to simply buying the xylitol and packaging it ourselves through either the UW Research Pharmacy or an outside pharmacy. Investigation revealed several problems with this plan; 1) the scale of the project is too large for the UW Pharmacy and 2) costs at outside vendors are prohibitive. We will therefore continue to work with Danisco/DuPont; the original 'pro-bono' agreement remains active

Preliminary research activities also included consultation by the PI and study team members with staff associated with the UW Clinical Research Unit to discuss clinical services to be utilized by the study. During this meeting, CRU lab activities were clarified along with discussion of training for CRU nursing staff on nasal irrigation and subsequent instructions to study subjects.

Study team members continue to correspond with staff associated with the UW Clinical Research Unit to review clinical services to be utilized by the study.

Study personnel have also been meeting regularly with DFM data personnel to develop the tracking database for study participants based on the course of study activities. The database will continue to be modified as the protocol proceeds through the human subjects recruitment and enrollment process.

Difficulties with the study relate to the human subject research approval process. Due to the complexity of engaging in human subjects research with veterans, the approval process has resulted in a more complex than usual progression of study activities. The complexity of this process was compounded by the unanticipated addition of the owner (DuPont) of the Xylitol manufacturing company (Danisco) and its human subjects research approval process.

An unanticipated problem with the research project was the long term leave of the assigned study coordinator due to health reasons. This resulted in impediment of study activities originally delegated to this individual. Specifically, completion of applications to the respective HS IRB and VA H&D Committee, refinement of study documents including consent/HIPAA forms, recruitment materials and outcome measures. Consequently, study tasks have been reassigned to UW Department of Family Medicine research administration staff. These staff members have proven to be up to the task of assisting in the development of the materials and progress above.

KEY RESEARCH ACCOMPLISHMENTS: As above regarding administrative issues; we continue to move as quickly as relevant human subjects related bodies allow.

REPORTABLE OUTCOMES: Provide a list of reportable outcomes that have resulted from this research to include:

- VA Research and Development Committee protocol approval
- UW HS IRB protocol approval
- Development of study tracking database
- Transition of relationship with private sector partner Danisco to Danisco-Dupont; Study related relationship is intact.

CONCLUSION: As stated, the purpose of this research effort is to evaluate the effects of two different types of nasal irrigation solution compared to a control group for sinus and fatigue symptoms in adults with GWI. General success for either form of NI compared to routine care would provide an immediately accessible treatment to improve the quality of life of veterans with GWI, CRS and fatigue. Because of the likely overlap between the underlying etiologies of CRS and fatigue between GWI vets and the general population, success may also translate to a more general population. Positive findings would suggest a number of important effects:

- Statistically positive results on HRQoL outcome measures would suggest that NI can provide effective adjunctive therapy for CRS and fatigue in adults with GWI, improving health of affected patients and potentially providing gains to society through reduced health care utilization and absenteeism related costs.
- Positive biomarker findings would contribute to our better understanding of the etiology of CRS and fatigue in the GWI population and of possible biological pathways underlying the NI efficacy.
- The finding that either form of NI is cost effective would provide economic justification for its clinical use.

REFERENCES: NA

APPENDICES:

Attachment A: UW HS IRB approval

Attachment B: VA Research and Development Committee approval



Health Sciences IRB

7/23/2012

Submission ID number: [2011-0843](#)

Title: Nasal Irrigation for Chronic Rhinosinusitis and Fatigue in Patients with Gulf War Illness(GW100054)

Principal Investigator: DEAN KRAHN

Point-of-contact: DIANA MYERS

IRB Staff Reviewer: JENNIFER FENNE

The convened HS IRB conducted a full review of the above-referenced initial application. The study was approved for the period of 12 months with the expiration date of 6/18/2013.

To access the materials approved by the IRB, including any stamped consent forms, recruitment materials and the approved protocol, if applicable, please log in to your ARROW account and view the documents tab in the submission's workspace.

If you requested a HIPAA waiver of authorization, altered authorization and/or partial authorization, please log in to your ARROW account and view the history tab in the submission's workspace for approval details.

Prior to starting research activities, please review the Investigator Responsibilities guidance (<http://go.wisc.edu/m0lovn>.) which includes a description of IRB requirements for submitting continuing review progress reports, changes of protocol and reportable events.

Please contact the appropriate IRB office with general questions: Health Sciences IRBs at 608-263-2362 or Education Research and Social & Behavioral Science IRBs at 608-263-2320. For questions related to this submission, contact the assigned staff reviewer.

**Department of
Veterans Affairs**

Memorandum

Date: July 16, 2012

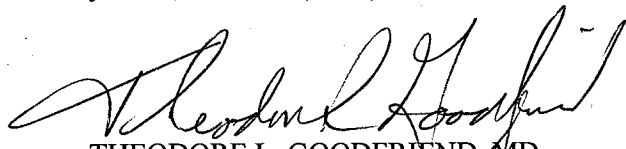
From: Associate Chief of Staff for Research

Subj: Research Protocol

To: Dean Krahn, MD, MS

1. Your protocol entitled "Nasal Irrigation for Chronic Rhinosinusitis and Fatigue in Patients with Gulf War Syndrome" (UW HS IRB #H-2011-0843) was initially reviewed and endorsed by the VA Research and Development Committee on May 1, 2012 (pending HIPAA authorization revisions and IRB and PO approvals).
2. The HIPAA authorization has been revised as requested.
3. The Privacy Officer and the Information Security Officer have approved the protocol.
4. This protocol was approved by the UW Health Sciences IRB on June 22, 2012. Please provide my office with a copy of the date-stamped consent form, when available.
5. The protocol was re-reviewed by the R&D Committee on July 10, 2012. The Committee voted to approved the protocol contingent on revision of the Study Participant letters to be printed on VA letterhead and to include Dr. Krahn's name and signature line. Those revised letters have been received. You may now proceed with this research.
6. If this project requires access to patient charts or other confidential records, please make arrangements for such access with the VA Research Office. Only people who are VA employees or have gone through the VA WOC process are eligible for access to VA medical records.
7. An enrollment log is attached to this memo for your use in recording the names of VA subjects or volunteers enrolled in this study. You will be asked to update this log and send it to the VA Research Office (Rm. C-3127) quarterly. (If you wish to do this via e-mail, contact Bev Birdsall at 280-7007). If signed consent forms are required, we are also required to have a copy of the signed consent form in the Research Office for all VA subjects or volunteers enrolled in VA-approved studies. Send or deliver copies of the consent forms to Bev Birdsall, VA Research Office, Room C-3127.
8. The R&D Committee also approved the acceptance of any funding that may accompany this study. If you intend to have funds for this study deposited in a VA account, contact Marvin Rupp (ext. 17801) to make arrangements.

9. **Please remember** that you must enter a note in each subject's CPRS medical record when you obtain consent and before you begin the experiment. If you enter normal, non-VA subjects in your research study, they must also be entered into CPRS.



THEODORE L. GOODFRIEND, MD

Attachments: Investigator Responsibilities Related to VA Research and the Protection of Human Subjects
Enrollment log

cc: Dr. Rabago
Terry Little
Jamie Swanlund
UW HS IRB/ARROW